substantially invade cells of a host and cannot spread substantially within infected cells and from infected to uninfected cells of the host and cannot produce toxins which will kill substantial numbers of the host's infected, as well as uninfected, cells.

Sub D1 cancel

REMARKS

Status of the Application

The issues raised in the Office Action dated October 31, 1995, are addressed below in paragraphs that correspond to the numbered paragraphs in the Office Action. Claims 11 and 12 have been cancelled without prejudice to or disclaimer of the subject matter. Claim 1 has been amended as discussed below in paragraph 4.

1. The Examiner has objected to the title as being non-descriptive. The title has been amended herein.

2. The Examiner has objected to the use of trademarks. The only example of a trademark provided by the Examiner is RPMI 1640. It is respectfully submitted that this term is not a trademark, but refers to a type of culture medium.

3. Applicants acknowledge the need to make references cited in the specification of record in order to have them considered by the Examiner.

4. Claims 1-12 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

(a) Claims 1-12 have been rejected as being vague and indefinite in the recitation of the term "substantially" and "substantial." This rejection is respectfully traversed.

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It is respectfully submitted that the use of the term "substantial" has been held to be acceptable by the courts as early as 1958. See Deering, Milliken & Co., Inc. v. Temp-Resisto Corp. et al., 116 U.S.P.Q. 386 (D. Ct. N.Y. 1958).

(b) Claims 1-12 have also been rejected as being indefinite in the use of the term "characterized." The claims have been amended to obviate this rejection.

5-6. The specification has been objected to and claims 1-13 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to teach one of ordinary skill in the art how to make/use the claimed invention.

Specifically, the Examiner has alleged that the specification fails to provide substantive guidance of how to use the modified *Shigella* as a vaccine. Further, it is alleged that the specification provides insufficient guidance for using the animal model to predict use in humans. This rejection is respectfully traversed. As is well established in law, the specification is presumed to be enabling. See In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The Examiner must provide reasons for doubting the truth or accuracy of any statement in the disclosure and has to back up the assertions with acceptable evidence or reasoning that is consistent with the contested statement. Sansonetti *et al.* has evaluated a double mutant of *Shigella* as a potential candidate for use in a vaccine. This mutant strain was able to provide protective immunity in macaque monkeys against a secondary challenge with *Shigella*.

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The Examiner seems to require human clinical data, which is contrary to current law. There is no decisional law that requires an applicant to provide data from clinical trials to establish enablement. Sansonetti *et al.* evidences that protective immunity is conferred in an art-recognized animal model. No reasons have been provided by the Examiner why one of ordinary skill in the art would doubt the results provided. The Examiner has provided no reasons to establish that no correlation exists between the utility claimed and the evidence presented. Nor has the Examiner provided any reasons why macaque monkeys are not art-recognized models. The C.C.P.A. has stated that "standard experimental animals" means whatever animal is usually used by those skilled in the art to establish the particular pharmaceutical application in question. In re Krimmel, 130 U.S.P.Q. 215, 219 (C.C.P.A. 1961).

Thus, in view of the art recognized *in vivo* data that presents a reasonable correlation between the utility claimed and the activity exhibited by the modified strains, it is respectfully submitted that the rejection should be withdrawn.

According to the Examiner, Sansonetti *et al.* states that "We believe that the macaque model provides indications, but no definitive answers on the suitability of a given strain for human vaccination." (Paper No. 2, page 3, lines 22-24.) The Examiner states that use of the claimed *Shigella* as a vaccine is therefore unpredictable. It is respectfully submitted that such a demand for evidence is contrary to the requirements of the law. The applicant does not have to prove

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that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does an applicant have to provide actual evidence of success in treating humans. In fact, the courts have repeatedly held that, all that is required is a reasonable correlation between the activity and the asserted use. Nelson v. Bowler, 206 U.S.P.Q. 881, 884 (C.C.P.A. 1980). In the instant case such a correlation has been established.

Further, it is alleged that the safety of the double mutants in humans is unclear. On this point, the Examiner's attention is drawn to Scott v. Finney, 32 U.S.P.Q. 2d 1115, 1120 (Fed. Cir. 1994) wherein the CAFC has stressed that therapeutic efficacy sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs.

It is submitted that Applicants have fully met all requirements under 35 U.S.C. § 112, first paragraph.

The Examiner also alleges that the specification does not provide a repeatable method for obtaining *Shigella* strains that contain the claimed inactivated genes. This rejection is respectfully traversed.

Applicants' invention is drawn to a method of producing modified *Shigella* strains containing inactivated genes, specifically genes that are involved in the invasion of cells and in cell-to-cell spread are inactivated. A combination of mutations gives rise to these modified *Shigella* that can be used as a vaccine. The specification teaches that the genes of the

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wild strain of *Shigella* may be wholly or partly removed, or permanently inactivated in any conventional manner. See pages 5-6. The specification discloses allelic exchange with *in vitro* mutagenized genes that have significant portions deleted.

Example 2 describes *in vitro* mutagenesis of the Shiga toxin A subunit gene that has been cloned into *E. coli*. *In vitro* mutagenesis was achieved by inserting the interposon Ω, which codes for spectinomycin resistance. The mutated gene was transferred into wild-type *S. dysenteriae*. Transformed clones expressing Tox^- phenotype were then identified.

Example 3 teaches the skilled artisan the construction of *S. dysenteriae* SC502 and SC503 from SC500 and SC501 by spontaneous cure, i.e. loss of their large virulence plasmid pHS7200, which is necessary for invasion of cells.

Example 4 discloses use of SC501 clone to construct a Tox^- strain with a mutation in the enterochelin gene "Ent^-", resulting in SC504.

Example 5 discloses the use of SC504 strain to construct a Tox^-, Ent^- and *ics*A clone SC504. The SC504 that is used is genetically engineered by *in vitro* mutagenesis of its *ics*A gene. The resulting clone, SC505, is Tox^-, Ent^-, and *ics*A^-.

Example 6 discloses a method of constructing an $aerobactin^-$ and *ics*A^- strain of *S. flexneri*. The resulting clone is SC506.

Finally, Example 7 teaches the skilled artisan construction of a $ToxA^-$, Ent^-, *ics*A^-, *S. dysenteriae* 1 clone. This clone is characterized by substantially reduced invasiveness, which makes it a suitable vaccine for humans against *S. dysenteriae*.

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Thus, the specification sets forth in detail the procedures for the construction of the claimed modified *Shigella* strains. Formation of SC500, SC501, SC502, SC503, SC504, and SC506 have been described. Despite this detailed description it is alleged that the specification is non-enabling. In making this assertion the Examiner has provided no reasons why the procedures of the specification are deemed "non-repeatable."

It is submitted that the Examiner has failed to establish a *prima facie* case of non-enablement. To make such a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. Angstadt, supra. In the instant application, examples provide step-by-step guidance to the skilled artisan for the formation of every claimed product. No reasons have been provided why these procedures fail to provide the skilled artisan adequate guidance.

Further, the Examiner is reminded that the mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. See M.P.E.P. § 608.01(P). In view of the extensive guidance provided by the specification and the background information which is present in the public domain, it is respectfully submitted that the Examiner has failed to establish that practicing the claimed invention would require "undue experimentation."

The above discussion makes it clear that the specification provides sufficient guidance to make the claimed strains.

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However, solely in an effort to expedite prosecution, applicants shall submit a declaration in conformance with the Budapest Treaty, attesting to the public availability of SC501, SC505, and SC506.

For the foregoing reasons, it is respectfully requested that the objection to the specification and rejection of the claims under 35 U.S.C. § 112, first paragraph be withdrawn.

7-9. Claim 13 has been rejected as being anticipated under 35 U.S.C. § 102(b) or in the alternative, as being obvious over Sekizaki *et al*. It is alleged that Sekizaki *et al*. disclose *Shigella* mutants that have lost the ability to produce high levels of Shiga toxin. It is alleged that the burden rests upon the applicant to show that these are distinct products. This rejection is respectfully traversed.

It is submitted that the method of obtaining the two products is a clear indication of the distinctiveness of the products claimed. Stx^- mutants of an Stx^+ *E. Coli* transductant are generated by random *in vivo* insertion mutagenesis with derivative transposons.

Examples 1 and 2 are drawn to the construction of SC501. The instant specification teaches that inactivation by transposons that are inserted into genes is not preferred because such inactivation can be lost by the genes when they are reproduced *in vivo* in subsequent *Shigella* generations. Thus, contrary to the process described by Sekizaki *et al*. wherein the mutant *Shigella* so produced may or may not preserve the Stx^- traits, the deposited SC501 *Shigella* strain is a product that

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will result in *Shigella* that has lost its ability to produce toxins.

This difference is an important distinction in the two products. The deposited strain consistently shows no toxin production, as opposed to the prior art method. For a prior art document to anticipate a claim it must disclose every element of the claim. Claim 13 is drawn to a deposited *Shigella* strain, a distinct product not disclosed by Sekizaki *et al.*

Further, the prior art fails to render the claimed *Shigella* obvious, because in view of the different characteristics and its inability to produce toxin, the claimed *Shigella* strain cannot be considered to be functionally analogous. Assuming, arguendo, that the Examiner equates the two strains functionally, it is submitted as discussed above that the claimed product shows superior properties in comparison to the *Shigella* disclosed by Sekizaki *et al.* and hence is unobvious over Sekizaki *et al.*

Claims 1-12 have been rejected under 35 U.S.C. § 103 as being obvious over Mills *et al.*, in view of Sekizaki *et al.*, Nassif *et al.*, Makino *et al.* and Ozenberger *et al.* Applicants' invention is directed to modifying *Shigella* to inactivate (1) a gene involved in the invasion of cells (e.g. aerobactin, enterobactin, enterochelin) and (2) a gene involved in the spread of *Shigella*. The combination of mutations results in a *Shigella* that can be used as a vaccine. Mills *et al.* do not suggest the mutant *Shigella* as claimed by Applicants. Mills *et al.* disclose (a) non-pathogenic *Shigella* attenuated by the

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introduction of a requirement for aromatic amino acids (aroD); (b) non-pathogenic *Shigella* attenuated by loss of the large plasmid that specifies bacterial invasion of the mucosal epithelium; (c) elimination of high level Shiga-toxin production from *S. dysenteriae* stains; and (d) hybrid strains consisting of a carrier organism, such as attenuated *Salmonella* or *E. coli*, carrying the gene encoding the *Shigella* O antigen polysaccharide. The types of vaccine described by Mills *et al.* do not characterize the location of such deletions and do not teach or suggest the combination of mutations claimed.

Sekizaki *et al.* merely teach generation of Stx (Shiga toxin) transposon mutants of *Shigella*. Nassif *et al.* teach a transposon mutant of *Shigella* that no longer produces aerobactin. Makino *et al.* disclose a *vir*G region on the 230 kb virulence plasmid of *S. flexneri* as required for cell-to-cell spread of the bacterium. Ozenberger discloses a method for creating deletion mutants in *E. coli*.

Thus, the only combination of mutations described in Mills *et al.* involves the aroD mutant combined with a mutation in the Shiga-toxin gene. Such a teaching does not disclose, teach, or suggest the claimed invention. As discussed above, the deficiencies of the primary reference are not cured by the secondary references because each of the cited references discloses individual mutations. The references do not motivate the skilled artisan to combine the teachings to obtain an effective vaccine against *Shigella*.

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The Examiner asserts that the "expected benefit of developing a vaccine" provides the requisite motivation to combine the teachings of the references. However, it is submitted that the Examiner is using improper hindsight in making this combination. "[O]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." In re Geiger, 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987). Further, "there must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references." In re Laskowski, 10 U.S.P.Q. 2d 1397, 1398 (Fed. Cir. 1989).

It is submitted that no such reason or motivation has been provided that supports the combination of primary and secondary references.

11. Claim 13 has been provisionally rejected under the judicially created doctrine of obviousness double patenting as being unpatentable over claim 39 of copending application Serial No. 08/118,100.

It is respectfully requested that the Examiner hold this rejection in abeyance until allowable subject matter has been indicated in either of the applications.

CONCLUSION

In view of the foregoing remarks, it is believed that this application is now in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No.

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06-0916. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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By _____
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